SYNTHESIS OF AMINOHYDROXYGLUTARIC ACIDS

BY

OSCAR TOUSTER

B. S., College of the City of New York, 1941

A. M., Oberlin College, 1942

AN ABSTRACT OF A THESIS

SUBMITTED IN PARTIAL FULFILLMENT OF THE REQUIREMENTS
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ACKNOWLEDGMENT

The author is indebted to Dr. Herbert E. Carter for his guidance and encouragement and for suggesting this investigation.

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Introduction

In the investigation of the structure of streptamine, a compound obtained by degradation of streptomycin, Carter and his associates (1, 2) isolated the dibenzoyl derivative of α,γ-diamino-β-hydroxyglutaric acid. It seemed that the synthesis of this compound might be facilitated by a study of the chemistry of α-amino-β-hydroxyglutaric acid (β-hydroxyglutamic acid), an amino acid formerly believed to be a constituent of proteins. Since the synthesis of α,γ-diamino-β-hydroxyglutaric acid would be a contribution to the synthetic approach to the structure of streptamine, and since β-hydroxyglutamic acid is of possible significance in biochemical investigations involving glutamic acid, a study of methods of synthesis of compounds of this type was undertaken.

Discussion of Results

The three aminohydroxyglutaric acids synthesized in this investigation were prepared by the catalytic reduction of derivatives of ethyl acetonedicarboxylate.

α,γ-Diamino-β-hydroxyglutaric acid was synthesized in poor yield by the high pressure reduction of ethyl α,γ-bis-(phenylazo)acetonedicarboxylate, with Raney nickel as catalyst and a mixture of acetic anhydride and ethyl acetate as solvent. The dibenzoyl derivative of this amino acid had a melting point several degrees below that of the α,γ-dibenzamido-β-hydroxyglutaric acid isolated in the degradation of streptamine and therefore probably has a different configuration from that of the natural compound. Other methods of preparing α,γ-diamino-β-hydroxyglutaric acid were studied, but the desired intermediates were not obtained. Dibenzamidoacetone was synthesized from a salt of diaminoacetone. However, neither dibenzamidoacetone nor diacetamidoacetone

was converted into an aldehyde by the action of formic acid esters and sodium alcoholates. Ethyl diazoacetate did not appear to condense with ethyl β-acetoxyacrylate or with ethyl β,β-diethoxyacrylate to form pyrazole or pyrazoline derivatives.

α-Amino-β,γ-dihydroxyglutaric acid was synthesized by the high pressure reduction of 3,5-dicarbethoxy-4-hydroxyisoxazole, with Raney nickel as catalyst and ethanol as solvent. The benzoyl derivative of this compound was obtained in the form of the lactone.

β-Hydroxyglutamic acid was synthesized in good yield by the high pressure reduction of ethyl α-phenylazoacetonedicarboxylate, with Raney nickel as catalyst and ethanol as solvent. In spite of reported difficulties in the synthesis of β-hydroxyglutamic acid by the low pressure reduction of ethyl α-oximinoacetonedicarboxylate with palladium and platinum catalysts (3), very satisfactory results were obtained by this method. The product obtained from the phenylazo compound, however, possessed somewhat different physical properties from β-hydroxyglutamic acid derived from the oxime. These differences are probably due to the diastereoisomeric composition of the preparations.

In experiments on the preparation of the benzoyl derivatives of glutamic acid and β-hydroxyglutamic acid, it was observed that incomplete benzoylation took place when the reactions were carried out in strong sodium hydroxide solution. The use of magnesium oxide, however, gave reaction mixtures which did not contain any free amino acid. This surprising behavior warrants further investigation.

Summary

α,γ-Diamino-β-hydroxyglutaric acid has been synthesized by high pressure reduction of ethyl α,γ-bis(phenylazo)-acetonedicarboxylate. The dibenzoyl derivative appears to have a different configuration from that of the α,γ-dibenz-

amido-β-hydroxyglutaric acid isolated in the degradation of streptamine.

α-Amino-β,γ-dihydroxyglutaric acid has been synthesized by high pressure reduction of 3,5-dicarbethoxy-4-hydroxy-isoxazole.

β-Hydroxyglutamic acid has been synthesized by high pressure reduction of ethyl α-phenylazoacetonedicarboxylate.

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VITA

The author was born on July 3, 1921, in New York, N. Y., where he received his elementary and high school education. He entered the College of the City of New York in September, 1937, and received the Bachelor of Science degree in June, 1941. He studied at Oberlin College the following year, receiving the Master of Arts degree in Chemistry in June, 1942. After spending a year and a half as a chemist with the Atlas Powder Company and five months as a Special Research Assistant in Chemistry at the University of Illinois, he worked as a research biochemist at Abbott Laboratories for a year and a half. In September, 1945, he returned to the University of Illinois as a Special Research Assistant in Chemistry. Since January, 1946, he has been a Special Research Fellow in Chemistry.

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